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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,021	03/19/2002	Philippe Gabant	VANM243.1APC1	5739

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EXAMINER

NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/031,021

Applicant(s)

GABANT ET AL.

Examiner

Dave T. Nguyen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 4, 6, 7 and 9-14 is/are pending in the application.
- 4a) Of the above claim(s) 9 and 11-13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4, 6, 7, 10, 14, and 15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Claims 1, 4, 6, 7, and 10 have been amended, and claims 14-15 have been added by the amendment filed June 14, 2004.

Claims 1, 4, 6, 7, 9-14 are pending.

Claims 9, 11-13 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Claims 1, 4, 6, 7, 10, 14, and 15, are pending for examination.

Claims 1, 4, 6, 7, 10 remain, and claims 14-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to:

1/ A genetically modified female mouse, whose genome comprises a homozygous mutation, a partially homozygous deletion or a totally homozygous deletion in the endogenous genetic sequence encoding the wild- type alpha-fetoprotein (AFP), wherein said genetically modified female mouse does not express a functionally active AFP, is sterile, and does not undergo a menstrual cyclization; and

2/ A method for identifying a candidate agent for use in treating osteoporosis, increasing fertility, or preventing conception comprising:

contacting the genetically modified female mouse of 1/ with a candidate agent;

determining the effects of said agent on osteoporosis, fertility or contraception in said genetically modified female mouse.

The specification is not enabling for claims directed to any other claimed embodiment within the elected claimed invention. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As set forth in the previous office action, the main thrust of the claimed invention is applicant's discovery of a nexus between a murine AFP and its role for female production and fertility (page, 3, par. 006). This discovery was based on the making of AFP knock-out mice (par. 008, working examples, wherein recombinant ES cells carrying the targeted allele were injected in C57BL/6J blastocysts (par. 0019), and wherein both heterozygous embryos and homozygous embryos/mice were produced. As the result of the making of these AFP knock-out mice, and further intercrosses, applicant has observed and concludes, particularly on the basis of AFP knock out homozygous mice and their subsequent intercrosses (page 9), that no pups were

obtained from this intercrosses, thereby suggesting an essential role of AFP for development and/or fertility (Table 2). Page 9 further states that “males homozygous for an *afp* disrupted allele appeared fertile and sired offspring but homozygous females never produce any live offspring”. An histological analysis was done on the AFP knock out homozygous females (*afp^{lacZ1/lacZ1}*) shows that (page 10) their homozygous tissues do not contain corpus lutea, the lack of which is indicative of the absence of ovulation (Figure 4). On the basis of this finding, Applicant further suggests on page 14 that “the *afp*^{-/-} phenotype corresponds to alive sterile females, which is a phenotype that may exist in the mouse population as well as in the human population. However, the claims as currently pending do not reflect such claimed embodiment. The claims still embrace a sterile female genetically modified mouse, wherein the mutated, deleted, or partial deleted AFP could still be expressed, and/or wherein only a heterozygous mutation, partial deletion, or a total deletion in one of the alleles, which contains the endogenous genetic sequence encoding the AFP. As set forth above, one of the essential element of the claimed invention is that the AFP protein must not be expressed as the result of a mutation or deletion of the endogenous AFP homozygously, and that only such essential element once achieved would cause sterility in female mice. As such, the claimed invention must necessarily require that AFP protein is null or non-expressible so as to disrupt the ovulation in the treated mice. Otherwise, it would require an undue experimentation for a skilled artisan to make and use the claimed invention as broadly claimed, whereby AFP is expressible, and yet the treated mouse is sterile as the result of the genetic modification in endogenous AFP coding sequence. Another issue is that

the claimed invention as currently pending does not recite that the genome of the claimed mouse comprises a homozygous mutation, a partially homozygous deletion or a totally homozygous deletion in the endogenous genetic sequence encoding the wild-type alpha-fetoprotein (AFP). In fact, claim 13 claims a genetically modified mouse, which is heterozygous for a mutation, a partial deletion or a total deletion in the endogenous genetic sequence encoding the wild type alpha-fetoprotein (AFP). However, there is no evidence that any useful phenotype can be effected by such a heterozygous AFP/- mouse. In fact, the specification on page 7 states that "phenotypically normal heterozygous mice *afp lacZ1/+* were generated and detected by Southern blot (see figure 1C)". Furthermore, the state of the art of transgenics is such that while one skilled in the art can disrupt a gene in mouse ES cells and produce a subsequent transgenic mouse by using the cloned ES cells, it is not reasonably predictable for one skilled in the art to produce a transgenic mouse that exhibits a desired phenotype, wherein the mouse has not been actually produced with a contemplated phenotype. In this instance, nowhere in the specification a reasonable skilled artisan could find any evidential support to demonstrate that a desired phenotype was generated as the result of a heterozygous AFP knock mouse. At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells (Polejaeva *et al.*, Theriogenology, Vol. 53, pages 117-126,

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2000; & Sigmund, 2000, *Thromb Vasc Biol.*, 20:1425-29). More specifically, Polejaeva *et al.* states:

Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

Thus, it is not apparent as to how one skilled in the art, without any undue experimentation, makes and uses genetically modified mice other than those as disclosed in the enabling embodiments, particularly on the basis of applicant's disclosure. As such, the claims are only reasonably enabling for claimed directed to the embodiments as indicated in the first paragraph of the stated rejection.

Applicant's response (page 5) has been considered by the examiner fully, but is not found persuasive for the reasons as set forth in above stated rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804**.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
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DAVE T. NGUYEN
PRIMARY EXAMINER